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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/914,426 | 01/07/2002 | Florence Nicolas | 8-1032-168 | 5423 |

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| EXAMINER | |
|---|---|
| MOHAMED, ABDEL A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1653 | |

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/914,426 | NICOLAS ET AL. | |
| | Examiner | Art Unit | |
| | Abdel A. Mohamed | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 January 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *13-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3, 1/7/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

## ACKNOWLEDGMENT OF PRIORITY, AMENDMENT, IDS, STATUS OF THE APPLICATION AND CLAIMS

1. This application filed under 35 U.S.C. 371 on 1/7/02 having a filing date of 3/1/00 of PCT/FR00/00513. Acknowledgement is made of Applicant's claim priority based on French Application Number 99/02727 having a filing date of 3/2/99. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119, which papers have been placed of record in the file. The preliminary amendment and the information disclosure statement (IDS) and Form PTO-1449 filed 1/7/02 are acknowledged, entered and considered. In view of Applicant's request claims 1-12 have been canceled and claims 13-34 have been added. Thus, claims 13-34 are pending in the application.

2. The specification is objected because there are no Headings disclosed in the disclosure and the following guidelines illustrate the preferred layout and content for patent application. These guidelines are suggested for the Applicant's use.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.

(b) CROSS-REFERENCE TO RELATED APPLICATIONS.

(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.

(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) Or

REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)

(e) BACKGROUND OF THE INVENTION.

(1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) BRIEF SUMMARY OF THE INVENTION.

(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).

(h) DETAILED DESCRIPTION OF THE INVENTION.

(i) CLAIM OR CLAIMS (commencing on a separate sheet).

(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).

(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a

nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

## STATEMENT OF STATUTORY BASIS, 35 U.S.C. 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 30-34 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). A "use" is not a proper.

## CLAIMS REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 13-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-29 are indefinite in the recitation "characterized in that" because the characterization of use can be recited by amending the claims to recite "wherein" or "comprising", etc. Thus, it is suggested that the term "wherein" or "comprising", etc. be replaced in the recitation thereof.

Claims 13, 16-18 and 20 are indefinite in the recitation "in that" in line 8 of claims 13 and 20, last line of claims 16 and 17, and in line 7 of claim 8 because the phrase "in that" appears to be superfluous in the claims as it does not serve to define and/or limit the collagenic peptide claimed. Deletion of this phrase is suggested, as it would not affect the scope of the claims.

Claims 13 and 24 are indefinite in the recitation "thiol functions" because it is not clear what the phrase "thiol functions" is intended to refer since the phrase is not defined in the specification or in the claims. Appropriate clarification is required.

Claim 13 is indefinite in the recitation "it" in line 10 because it is unclear if the term "it" is referring to the thiol function or the collagenic peptide.

Claims 13, 22 and 24 are indefinite in the recitation "and/or" because it is not clear if the "and" or the "or" is the limiting language. Appropriate clarification is suggested.

Claims 14, 16, 18 and 21 are indefinite in the recitation "at least some" because it is not clear how many is some? It could be less than 1. Appropriate clarification is required.

Claims 14, 16 and 18-20 are indefinite in the recitation "$[-CR_2^{0-}]_x$" because there are no definitions for $R_2$ nor for $R^0_2$ and it is not clear if the claims are intended to refer to $R^0$ or $R_2$ or $R^0_2$ or $(CR^0)_2$. Similarly claim 14 in Formula (II) recites "$[-CR_2^{00-}]_y$" which is not defined and it is not clear if it intended to refer to $R_2^{00}$ or $R_2$ or $R^0_2$. Appropriate clarification is required.

Claim 14 is indefinite in the recitation "preferably" and "even more preferably" because these phrases make the choice "optional". If an ingredient, a step, or other structural element is truly optional (e.g., preferably this or even more preferably that), i.e., its presence is not necessary for attainment of the result that is an object of the invention, then recitation thereof does not belong in the claim.

Claim 15 is indefinite in the recitation "the grafted mercaptoamino residues are chosen from the following group of radicals..." because it is not clear if Applicant intends a Markush format. If Applicant intends to use a Markush format, then, the Office recommends the use of the phrase ".....selected from the group consisting of ....." in listing species to ensure the Markush group is "closed".

Claims 15, 25 and 26 are indefinite in the recitation the extraneous periods of l.1, l.2 and l.3 in claim 15, 1., and 2., in claim 25, and 1., 2., and 3., in claim 26, respectively because the periods are not essential.

Claims 16 and 17 are indefinite in the recitation "it is crosslinkable" because it is not clear to what the term "it" is referring. Appropriate clarification is required.

Claims 17, 19 and 20 are indefinite in the recitation "or a cation capable of forming a salt with $COO^-$" because the term "capable" makes the claims unclear as to whether the cation forms a salt with $COO^-$ or not. Amendment of the claims to recite "or a cation which forms a salt with $COO^-$" is suggested.

Claims 21 and 22 are indefinite in the recitation "G being an acyl comprising.....". It appears that after an acyl a word is missing. If the missing word is "group". Amendment of the claims to recite "G being an acyl group comprising....." is suggested.

Claim 22 is indefinite in the recitation "comprising hetero atoms (advantageously O and/or N)" because the phrase "advantageously" and the parentheses appear to be superfluous for the same reasons discussed under the rejection of claims 13, 16-18 and

20 above. Thus amendment of the claim to recite "comprising hetero atoms which are O or N" would obviate this rejection.

Claim 23 is indefinite in the recitation "G is an acyl being chosen from....." because it is not clear if Applicant intends a Markush format. If Applicant intends to use a Markush format, then, the Office recommends the use of the phrase "....selected from the group consisting of ....." in listing species to ensure the Markush group is "closed".

Claim 23 is also indefinite in the recitation "such that the molecular weight of the polymer chain is between 100 and 15 000" because it is not clear if the molecular weight is in Dalton or Kilo Dalton. Further, the recitation of "15 000" is confusing because it is not clear if coma (,) or other number is missing between the space 5 and 0. Appropriate clarification is required. Further, the phrase "such that" appears to be superfluous. Deletion of the phrase is suggested.

Claim 24-16 are indefinite and confusing in the recitation "consists essentially in reacting in solution exclusively the carboxylic functions of the aspartic acids and glutamic acids of collagenic peptide" because it is not understood how exclusively the carboxylic functions of the aspartic and glutamic acids react in a solution. It is not clear how a person of skill in the art can put only (i.e., exclusively) the carboxylic functions of the aspartic and glutamic acids in solution and leave out the rest. Appropriate clarification is required.

Claims 24 and 26 are indefinite in the recitation "chosen from the group comprising products that activate carboxylic groups" because the language in the claims appears to be in appropriate since there is no *per se* groups. Further, there is inconsistency between "group" and "groups". Appropriate correction is suggested.

Claims 25 and 26 are indefinite in the recitation "(conversion to thiols)" because it appears the enclosed material in the parentheses is not essential to the sentence of the claims and that if not included would not alter the meaning of the claims. Thus, deletion of the parentheses, i.e., the enclosed material (conversion to thiol) or if the enclosed material is needed, amendment of the claims to recite (by conversion to thiol" is suggested.

Claim 26 is indefinite and vague in the recitation "and possible carboxylic function are blocked" because it is not clear how the blockage of the carboxylic functions is determined. Appropriate clarification is suggested.

Claims 26-29 are indefinite in the recitation "so as" because the phrase "so as" appears to be superfluous in the claims as it does not serve to define and/or limit the collagenic peptide claimed. Deletion of this phrase is suggested as it would not affect the scope of the claims.

Claims 27-29 are indefinite and confusing in the recitation "an additional step F is envisaged" and "this step F...." because there are no disclosure or recitation of steps A-E in claims 24-29. Thus, there is no proper antecedent basis for "step F" in claims 24-29. Appropriate correction is required.

Claims 27-29 are indefinite in the recitation "grafts G" because there is no proper antecedent basis for the phrase "grafts G" in independent claims 24, 25 and 26 and dependent claims 27, 28 and 29, respectively.

Claims 27-29 are also indefinite in the recitation "grafts G that are different in nature" because it is not clear how they are different. Appropriate clarification is required.

Claims 30-34 are indefinite in the recitation "which is a constituent of implants" because it is not clear whether the claims are referring to the biomaterial or the peptide. Appropriate clarification is required.

Claims 30-34 provide for the use of collagenic peptides as biomaterials according to claim 13, claim 24, claim 25, claim 26 and claim 27, respectively; but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process Applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

## CLAIMS REJECTION-35 U.S.C. § 103(a)

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35

U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gagnieu et al. (U.S. Patent No. 5,763,579) taken with Gagnieu (U.S. Patent No. 5,412,076) and Lin et al. (Biochem. Biophys. Acta, Vol. 1038, No. 3, pp. 382-385)

The reference of Gagnieu et al. ('579 patent) teaches similarly as the instantly claimed invention a collagenic peptide modified by grafting which is soluble in water and/or polar organic solvents and which comprises free or substituted thiol functional groups carried by residues of cysteine or its derivatives, wherein said collagen is crosslinkable by formation of disulfide bridges in the presence of oxidants, and process for production and use thereof (See e.g., abstract, and cols. 3 to 10) as directed to claims 13-29. Further, the general formula disclosed on col. 5 corresponds to the claimed Formula I, for example X and $R_1$ are same in both situation (i.e., X = 1 or 2, $R_1$ is hydrogen hydrocarbon radicals, etc.)

The reference of Gagnieu et al. ('579 patent) differs from claims 13-29 in not teaching the substitution of the free carboxylic functions of the glutamic and aspartic acids of the collagenic chain via amide bonds and the use of graft G which is an acyl comprising a hydrocarbon species such as carboxylic groups e.g., carbodiimides. Although, the '579 patent dose not teach the exclusive grafting of mercapto-amino radicals onto the Asp and Glu acids of the collagen chain; however, on col. 9, lines 48 to col. 10, lines 15 suggests by stating that the general conditions of this reactions are deduced from rules which are defined in peptide synthesis and which depends on the type of protection and activation used. It is advantageously in a quantity sufficient to neutralize the carboxylic functional groups of the acid residues of collagen (aspartic and

glutamic acids of collagen), as well as the acidic products optionally formed during grafting, and concludes by stating that the adjustment of these parameters (i.e., grafting of mercaptoamino radicals onto aspartic and glutamic acids of the collagenic chain) is an operation which is within the capability of a person skilled in the art for the field considered to obtain either a modified collagen or a precursor of collagen SH.

The secondary reference of Gagnieu ('076 patent) teaches a modified collagen that is useful as a biomaterial for prostheses, implants or other medical items, which is soluble in water and/or polar organic solvents, and contains free or substituted thiol functions carried by residues of cysteine or derivatives thereof bonded to the collagen via spacer compounds (See e.g., abstract and col. 4). The residues are grafted onto the carboxylic of glutamic and aspartic amino acids, present in the starting collagen (See e.g., col. 5, lines 28-33 and col. 7, lies 58-63). The residues are grafted by means of amide bonds (See e.g., steps c and d of col. 6 which are typical conditions for forming an amide bond). Further, the general formula disclosed on col. 8 corresponds to the claimed Formula I, for example X, $R_1$ and $R_2$ are same in both situation (i.e., X = 1 or 2, $R_1$ is hydrogen hydrocarbon radicals, $R_2$ is an aliphatic and/or aromatic, etc.). Also, the formula disclosed on col. 9, lines 25-30 is the same as Formula 1.2 claimed in claim 15. Furthermore, on col. 7, the '076 patent discloses collagenic peptide comprising graft G which is an acyl having a hydrocarbon based species and a process for obtaining and/or reacting the carboxylic functions of the aspartic and glutamic amino acids and acylation of the free amine functions and of the collagenic chains as directed to claims 21-24 and 27-29. On col. 6, the reference discloses the steps of deprotection and oxidation in a process for preparing a crosslinkable collagenic peptide as directed to claims 25 and 26. Moreover, acylation and coupling reactions of amine functions with carboxylic sites belonging to proteins are known to those skilled in the field of protein

biochemistry as acknowledged on page 22, lines 16-24 in the instant specification. Further, the reference of Lin et al. describes a two-step procedure for introduction of sulfhydryl groups at protein carboxyl groups, wherein the first step is a carbodiimide mediated addition of cystamine, which contains a disulfide function. The second step is reductive generation of the free sulfhydryl group. Thus, the reference clearly shows that the sulfhydryl group incorporation scheme can be used to introduce sulfhydryl groups directly to proteins (See e.g., page 382 and 384-385).

Therefore, in view of the above and in view of the combined teachings of the prior art, one of ordinary skill in the art at the time the invention was made would have been motivated to employ a collagenic peptide modified by grafting free or substituted thiol functions, which is soluble in water and/or polar solvents, carried by mercaptoamino residues, wherein said mercaptoamino residues are exclusively grafted onto the aspartic and glutamic acids of the collagenic chain via amide bonds, and the collagen is crosslinkable by formation of disulfide bridges in the presence of oxidants, and process for production and use thereof, absence of sufficient objective factual evidence or unexpected results to the contrary.

## CONCLUSION AND FUTURE CORRESPONDANCE

6. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S.F. Low can be reached on (571) 272-0951. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Christopher S. F. Low

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AAM Mohamed/AAM

February 3, 2004